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Abbreviations

FEV_1: Forced expiratory volume in one second

MAAS: Manchester Asthma and Allergy Study

NO_2: Nitrogen dioxide

PM_{10}: Particulate matter with an aerodynamic diameter less than 10μm

sR_{aw}: Specific airways resistance

ABSTRACT

Background: Findings from previous studies on the effect of air pollution exposure on lung function during childhood have been inconsistent. A common limitation has been the quality of exposure data used and few studies have modelled exposure longitudinally throughout early life.

Objectives: To study the long term effects of particulate matter with an aerodynamic diameter <10μm (PM_{10}) and nitrogen dioxide (NO_2) exposure on specific airway resistance (sR_{aw}) and forced expiratory volume (FEV_1) before and after bronchodilator treatment within the Manchester Asthma and Allergy Study (MAAS) birth cohort (N=1185).

Methods: Spirometry was performed during clinic visits at ages 3, 5, 8 and 11 years. Individual level PM_{10} and NO_2 exposures were estimated from birth to age 11 through a microenvironmental exposure model. Longitudinal and cross-sectional associations were estimated using generalized estimating equations and multivariable linear regression models.

Results: Lifetime exposure to PM_{10} and NO_2 was associated with significantly less growth in FEV_1 (% predicted) over time, both before [-1.37% (95% CI: -2.52, -0.23) for a 1-unit increase in PM_{10} and -0.83% (95% CI: -1.39, -0.28) for a 1-unit increase in NO_2] and after bronchodilator treatment [-3.59% (95% CI: -5.36, -1.83) and -1.20% (95% CI: -1.97, -0.43), respectively]. No association was found between lifetime exposure and sR_{aw} over time. Cross-sectional analyses of detailed exposure estimates for the summer and winter prior to age 11 and lung function at age 11 indicated no significant associations.

Conclusions: Long term PM_{10} and NO_2 exposures were associated with small, but statistically significant, reductions in lung volume growth in children of elementary school age.

INTRODUCTION

Lung function is an important indicator of respiratory health and long term survival (Hole et al. 1996). Unlike information collected through questionnaires, measured lung function is an objective health outcome that is not affected by recall or reporting bias. The respiratory tract is at risk from air pollution, as gaseous pollutants and small particles in the air are inhaled through the nose and mouth. Two air pollutants frequently studied are nitrogen dioxide (NO_2) and particulate matter (PM). Both are derived from traffic related sources, but are also generated within the home, for example by gas cookers and cigarette smoke. Both of these pollutants have been associated with respiratory and cardiovascular morbidity and mortality (Brunekreef et al. 2002). Several cross-sectional and longitudinal studies have been carried out on the association between NO_2 and PM exposure and lung function in children. However, results of these studies have been disparate and conclusions inconsistent. While some studies reported associations with lung volume only (Raizenne et al. 1996; Rojas-Martinez et al. 2007; Sugiri et al. 2006), others reported associations with expiratory flow only (Avol et al. 2001; Oftedal et al. 2008). Other studies reported associations with both lung volume and flow (Gauderman et al. 2000; Horak et al. 2002; Schwartz 1989), while others reported no associations at all (Dockery et al. 1989; Hirsch et al. 1999; Neas et al. 1991; Nicolai et al. 2003). In a recent review of studies on air pollution and lung function, the authors concluded that it was not possible to perform formal quantitative comparisons of findings, due to the heterogeneity of study designs (Götschi et al. 2008).

One limitation common to many previous studies is the assessment of exposure to air pollution. Most previous studies of the effects of air pollution on lung development in children have estimated associations with current air pollution exposure, i.e. the average concentration over the

previous 12 months, rather than lifetime exposure or early life exposure (Oftedal et al. 2008), and have estimated exposures based on measurements from central monitoring stations located near the child's residence, without accounting for geographical factors (Hirsch et al. 1999; Nicolai et al. 2003; Oftedal et al. 2008), indoor as well as outdoor exposures, or time-activity patterns.

We have developed a novel Microenvironmental Exposure Model (MEEM) (Mölter et al. 2012), which allows for spatial (indoor and outdoor microenvironments) and temporal variability in pollutant concentrations (Mölter et al. 2010a; Mölter et al. 2010b) and incorporates children's time-activity patterns to predict personal exposure. The performance of MEEM (for NO_2) was evaluated previously through a personal monitoring study of 46 12-13 year old schoolchildren in Manchester (Mölter et al. 2012); we found good agreement between modelled and measured NO_2 concentration (e.g. mean predictor error=-0.75; Normalised mean bias factor=0.04; Normalised mean average error factor= 0.27; Spearman's rank correlation=0.31, $p<0.05$) This performance evaluation also demonstrated that MEEM provided better estimates of exposure than central monitors or an outdoor air pollution model, which tended to overestimate personal exposure levels (Mölter et al. 2012).

The aim of the present study was to estimate the associations of modelled PM_{10} (particulate matter with an aerodynamic diameter <10μm) and NO_2 exposure with lung function in elementary school children enrolled in a population based birth cohort - the Manchester Asthma and Allergy Study. Exposures and lung function were evaluated longitudinally throughout childhood. In addition, we applied a more detailed exposure model in a cross-sectional analysis of lung function measured at age 11 years.

METHODS

Study population

The children studied were participants of the Manchester Asthma and Allergy Study (MAAS). MAAS is an ongoing prospective birth cohort based in Manchester, UK. The cohort initially comprised 1185 children of mothers who were recruited during pregnancy at two local hospitals between 1995 and 1997 (Simpson et al. 2001). Children attended review clinics at ages 3, 5, 8 and 11 years, which included pulmonary function tests and skin prick tests for common inhalant and food allergens. In addition, parentally completed questionnaires were collected at each review (Custovic et al. 2002; Custovic et al. 2004). MAAS received ethical approval by the Local Research Ethics Committee (SOU/00/258; SOU/00/259) and written informed consent was provided by the parents.

Definition of outcomes: Lung function

All pulmonary function tests were carried out by trained technicians at Wythenshawe Hospital, Manchester. The most informative test to measure lung function was selected for each age group (Beydon et al. 2007; Bisgaard et al. 1995; Dab et al. 1976).

Specific airways resistance (sR_{aw}) was measured at ages 3, 5, 8 and 11 years, using a constant volume whole-body plethysmograph (Masterscreen Body 4.3; Erich Jaeger Gmbh, Würzburg, Germany) (Lowe et al. 2002; Nicolaou et al. 2008). High values of sR_{aw} indicate poor lung function. Forced expiratory volume in one second (FEV_1) was measured at ages 5, 8 and 11 years using a pneumotachograph based spirometer (Erich Jaeger Gmbh, Würzburg, Germany). The protocol for measuring FEV_1 was in accordance with American Thoracic Society Guidelines (American Thoracic Society 1995). All children were asymptomatic at the time of testing and

β2-agonists were withheld for at least 4 hours prior to testing. The test was repeated at intervals of 30 seconds until 3 technically acceptable traces were obtained, the highest two of which were within 5% of each other. The percent predicted FEV_1 was calculated using reference equations developed by the Asthma UK Collaborative Initiative (Stanojevic et al. 2009). Post-bronchodilator FEV_1 was measured at age 5 and 11 years by repeating the FEV_1 measurement 15 minutes after inhalation of 400μg of albuterol. Results were analysed as percent predicted FEV_1.

Definition of exposures: Modelled PM_{10} and NO_2 exposure

The exposure estimates in this study are based on the concept of microenvironments (ME) - a defined space with a homogenous pollutant concentration (Ott 1982). MEs can represent spaces outdoors or indoors and different methods can be used to estimate concentrations in different types of microenvironments. The microenvironmental models used in this study assumed that children spend the majority of their time in three types of MEs: home, school and the journey between home and school.

Information on children's home and school addresses from birth to age 11 was collected through a parental questionnaire, completed at the age 11 review. In this questionnaire parents were asked to list the dates and addresses for all homes the child had lived in and each school the child attended, the mode of transport between each home and respective schools. These data were entered into a SQL database (MS SQL2008R2) to create a timeline for home and school addresses from birth to age 11 for each child. In addition, the shortest driving route between each home and school was estimated using the network analyst extension of ArcGIS9.2.

Figure 1 summarizes the methods used to estimate NO_2 and PM_{10} concentration in each microenvironment. Concentrations for outdoor MEs (i.e. Home outdoor ME, School outdoor

ME, Journey outdoor ME) were estimated using land use regression models, as described in detail elsewhere (Mölter et al. 2010a; Mölter et al. 2010b). In brief, land use regression models were developed using estimated annual mean NO_2 and PM_{10} concentrations at 208 locations derived from an air dispersion model. The final land use regression models mainly comprised traffic related predictor variables, such as vehicle counts on major roads, and had determination coefficients (R^2) of 0.71. Performance evaluations using a set aside dataset (70 locations) and concentrations measured at automatic monitoring stations showed an acceptable level of agreement (R^2 range: 0.33-0.86). To model children's exposure from 1996 to 2008 the above LUR models were recalibrated to provide thirteen annual models for PM_{10} and NO_2, respectively (Mölter et al. 2010b): data from the air dispersion model and the UK year adjustment calculator were used to estimate annual PM_{10} and NO_2 concentrations from 1996 to 2008 at the 278 receptor sites described above. These concentrations were entered into regression analyses that included the same predictor variables used in the original LUR models. This resulted in individual models for each year; all models used the same predictor variables but generated different coefficients. A performance evaluation of these models against monitored data showed good agreement (R^2 range: 0.35-0.97, RMSE range: 1.8-8.3)(Mölter et al. 2010b).

Concentrations for Journey indoor MEs (i.e. inside cars or buses) and School indoor MEs were estimated based on indoor to outdoor (I/O) ratios published in the literature (International Center For Technology Assessment 2000; Stranger et al. 2008). Concentrations in the Home indoor MEs were estimated using I/O ratios or a mass balance model (INDAIR), depending on the time period being modelled (Dimitroulopoulou et al. 2006). This resulted in two slightly different models: the Microenvironmental Exposure Model (MEEM) and the Lifetime model (Figure 1).

MEEM was used to estimate each child's exposures during the summer and winter prior to the age 11 review visit (Mölter et al. 2012). We modelled winter and summer exposures separately to capture variation in home indoor air concentrations due to seasonal differences in air exchange rates. In MEEM Home Kitchen ME, Home Living room ME and Home Bedroom ME concentrations were estimated individually using the INDAIR model, a validated mass balance model, designed specifically to estimate indoor concentrations of NO_2 and PM_{10} concentrations within residential buildings in the UK (Dimitroulopoulou et al. 2001; Dimitroulopoulou et al. 2006).

A parental questionnaire administered at the child's age 11 review was used to collect input parameters for the INDAIR model, such as room sizes, air exchange rates, and the presence of indoor sources of NO_2 and PM_{10}. The indoor sources included in the model were gas cooking and cigarette smoke, which are considered to be the main sources of NO_2 and PM_{10} inside homes in the UK (Coward et al. 2001; Berry et al. 1996). In addition, the questionnaire collected time-activity data used to estimate the timing and duration of time in each microenvironment. Therefore, MEEM provided spatially resolved time-weighted exposure estimates for each child.

The performance of MEEM was evaluated using a personal monitoring study of schoolchildren (age 12-13) attending a local secondary school in Manchester (Mölter et al. 2012). MEEM performed well, when compared with NO_2 concentrations measured with personal monitors (Ogawa passive samplers), with a mean prediction error of -0.75μg/m³. A paired analysis of measured and predicted concentrations showed no significant difference between measured concentrations and MEEM estimates (Wilcoxon's signed rank test: $Z=-0.05$, $p=0.96$).

Input parameters for the INDAIR model were available for the current (age 11) home of each child, but the majority of children had moved at least once since birth. Therefore, we used a simplified Lifetime model to estimate the average PM_{10} and NO_2 exposure of each child for each month from birth to age 11. In contrast with MEEM the Lifetime model used an I/O ratio to calculate exposure inside the home, instead of using the INDAIR model and it assumed that all children were in the School indoor ME from 9am to 3pm. However, as for MEEM, outdoor ME exposures (i.e. Home outdoor ME, School outdoor ME, Journey outdoor ME) were estimated using land use regression models, and Journey indoor MEs (i.e. inside cars or buses) and School indoor MEs were estimated based on (I/O) ratios.

Definition of potential confounders

Potential confounding variables and covariates were identified based on previous research within MAAS and previous publications (Lowe et al. 2002; Lowe et al. 2004; Nicolaou et al. 2008; Oftedal et al. 2008) and included gender, age, ethnicity, older siblings, sensitisation, asthma or current wheeze, family history of asthma, parental smoking, parental atopy, day-care attendance during the first two years of life, hospitalisation during the first two years of life, presence of a gas cooker in the home, presence of a dog or cat in the home, visible signs of dampness or mould in the home, body height, body weight, body mass index, maternal age at birth, gestational age, duration of breast feeding, Tanner stage (age 11 only) and socioeconomic status (paternal income). In addition, average PM_{10} and NO_2 concentrations over three days prior to the child's review visit were collected from four (for PM_{10}) or five (for NO_2) urban background monitoring stations across the Greater Manchester area (Oftedal et al. 2008).

We classified children as having current wheeze based on a positive response to the question "Has your child had wheezing or whistling in the chest in the last 12 months?", and classified them as having asthma based on positive answers to at least two of the following three variables: doctor diagnosis of asthma ever; current wheeze; asthma medication during the previous 12 months, consistent with the GA^{2}LEN definition of asthma (Carlsen et al. 2006; Haland et al. 2006). At each review potential allergic sensitisation to common inhalant and food allergens was determined through skin prick tests for inhalant allergens (mites, cat, dog, mould, grass pollen, and tree pollen) and food allergens (milk, egg, and peanut). All allergens were tested at each review with the exception of tree pollen and peanut allergens, which were tested at the age 8 and age 11 reviews only. Children were classified as having atopy, if they had at least one positive skin prick test (defined as a mean wheal diameter 3mm greater than the negative control). Parental atopy was also established through skin prick tests, which were carried out during the recruitment stage.

Statistical analysis

All analyses were carried out with SPSS 16.0 (SPSS Inc). Prior to all analyses sR_{aw} was ln-transformed as it follows a log-normal distribution. FEV_1 and post-bronchodilator FEV_1 were not transformed as these variables were normally distributed. Multivariable linear regression was used to cross-sectionally estimate associations of PM_{10} and NO_2 exposure during the summer and winter prior to age 11 (estimated by MEEM) with sR_{aw} and FEV_1 at age 11 years. All potential confounders were entered individually into bivariate models with the exposure and outcome variables, and potential confounders that were significant predictors of the outcome ($p<0.05$) were evaluated using multivariate stepwise analyses that retained only covariates that significantly predicted the outcome, or that were retained *a priori* (age and gender in all sR_{aw}

models, Tanner stage for all models of outcomes at age 11). Models of FEV_1 outcomes were not adjusted for age, gender and body height, as these factors were used to calculate the percent predicted values. Models of MEEM exposures at age 11 were not adjusted for cigarette smoking, as information on smoking was already included in the INDAIR model.

The association between lifetime exposure and the development of lung function was analysed using generalised estimating equations to account for the within subject correlation of repeated measures, with the same covariates included in the cross-sectional models. Monthly exposures averaged into the following time windows: sR_{aw}- age 0-3, age 3-5, age 5-8, age 5-11; FEV_1 – age 0-5, age 5-8, age 8-11; FEV_1 after bronchodilator treatment – age 0-5, age 5-11. For completeness exposure estimates from the lifetime exposure model were also analysed cross-sectionally against lung function at ages 3, 5, 8 and 11 years. For these analyses the monthly exposure estimates were averaged into the following time windows: first year of life (age 0-1), birth to review ages (age 0-3, age 0-5, age 0-8, age 0-11), one calendar year prior to reviews (age 2-3, age 4-5, age7-8, age 10-11). The level for statistical significance was set at $p<0.05$.

RESULTS

Participants and descriptive data

Participant flow with numbers of individuals at each stage of the study, the number of lung function measurements collected and the number of exposure estimates available is shown in Figure 2. Descriptive statistics of the study population and the covariates included in the final models are presented in Table 1; descriptive statistics of potential confounders not included in the final models are shown in Table S1 (Supplemental Material). As expected, the prevalence of atopy increased from age 3 to age 11, while the prevalence of asthma or current wheeze

remained fairly constant during this time period. A complete dataset of FEV_1, pollutant exposures and covariates at two or more reviews was available for 342 children (Table 1). Children included in the longitudinal analysis of the effect of PM_{10} and NO_2 exposure on the change in FEV_1 were more likely to be female and were less likely to have asthma or wheeze in early life. By age 8 years there were no differences in asthma/wheeze between children with full sets of longitudinal data and those without. Table 2 summarises the lung function measurements at each age. The mean FEV_1 increased from 1.05l at age 5 to 2.30l at age 11 years, resembling typical values for Caucasian children of these ages (Stanojevic et al. 2009).

Exposure to pollutants

Figures S1-S2 (Supplemental Material) describe the distribution of the exposure estimates by pollutant and exposure time window. MEEM predicted higher PM_{10} and NO_2 exposures during the winter than during the summer (Supplemental Material, Figures S1 and S2) and it predicted a wider range of exposures than the Lifetime model. The lifetime exposure estimates decreased from age 0-1 to age 10-11 (Supplemental Material, Figure S1-S2), which most likely reflects the general decrease of PM_{10} and NO_2 levels in the Greater Manchester area from 1996 to 2008 (DEFRA 2009). PM_{10} and NO_2 exposures were moderately to strongly correlated in all exposure time windows (Pearson's r=0.59-0.89).

Association between exposure to pollutants and sR_{aw}

The results of the cross-sectional analyses conducted at ages 3 to 11 years are shown in Table S2 in the Supplemental Material. Table S2 indicates a significant negative association between PM_{10} exposure during early life and sR_{aw} at age 3 and 5 years. However, all other analyses showed no statistically significant associations. Furthermore, at age 11 years there was no association

between PM_{10} and NO_2 exposure (MEEM) during the summer or winter and sR_{aw} (Table 3) and there was no association between lifetime exposure and longitudinal sR_{aw} (Table 3).

Association between exposure to pollutants and FEV_1

In the cross-sectional analysis at age 11 years, there was no association between PM_{10} and NO_2 exposure (MEEM) during the summer or winter and FEV_1 % predicted (Table 3). In contrast, the longitudinal model of lifetime exposure to pollutants and longitudinal measures of FEV_1 revealed a significant association between exposure to pollutants and the change in this measure of lung function during childhood. PM_{10} and NO_2 exposures were associated with poorer lung function over time (PM_{10}: β=-1.37, 95%CI: -2.52,-0.23; NO_2: β=-0.83, 95%CI: -1.39,-0.28). Based on the average predicted FEV_1 within MAAS at ages 5, 8 and 11 of 1.65l (see Table 2), the model estimated that for each unit increase (1μg/m³) in PM_{10} exposure, the growth in FEV_1 from age 5 years to 11 years was 23ml smaller, and for each unit increase (1μg/m³) of NO_2 exposure, the growth in FEV_1 was 14ml smaller [$\Delta FEV_1(ml)=\beta/100*1.65*1000$]. For completeness results of cross-sectional analyses conducted at other time points are shown in Table S3 (Supplemental Material). Table S3 shows no statistically significant association between PM_{10} or NO_2 exposure windows and FEV_1 on cross-sectional analyses.

Association between exposure to pollutants and post-bronchodilator FEV_1

At age 11 years, there was no association between PM_{10} or NO_2 exposure (MEEM) during the summer or winter and post bronchodilator FEV_1 % predicted (Table 3). However, there was a significant negative association between post-bronchodilator FEV_1 and the annual average NO_2 exposure from age 10-11 years estimated by the lifetime model (β=-1.00, 95% CI:-1.96,-0.03,p=0.043). In the longitudinal models, we observed a significant negative association

between post-bronchodilator FEV_1 and PM_{10} and NO_2 exposure over time (PM_{10}: β=-3.59, 95%CI:-5.36,-1.83; NO_2: β=-1.20, 95%CI:-1.97,-0.43). Based on the average predicted FEV_1 of 1.65l (see above), these would be equivalent to a growth deficit in post bronchodilator FEV_1 of 59ml from age 5 years to 11 years per unit increase in PM_{10}, and a growth deficit of 20ml from age 5 years to 11 years per unit increase in NO_2. For completeness results of cross-sectional analyses conducted at other time points are shown in Table S4 (Supplemental Material). Table S4 shows significant negative associations between post-bronchodilator FEV_1 and early life PM_{10} ($\beta_{Age\ 0\text{-}1}$=-3.00, 95% CI:-5.29,-0.71; $\beta_{Age\ 0\text{-}5}$=-4.70, 95% CI:-7.85,-1.55) and NO_2 exposures ($\beta_{Age\ 0\text{-}1}$=-0.91, 95% CI:-1.77,-0.05).

DISCUSSION

To our knowledge this is the first study to estimate the effect of modelled individual lifetime exposure to PM_{10} and NO_2, from birth through elementary school, on the development of lung function measured throughout childhood. Modelling both exposure and lung function longitudinally, our results indicated a small, but statistically significant, impairment in growth of FEV_1 with an increase in exposure to air pollutants. We estimated the size of this effect to be a loss of 23ml in the growth in FEV_1 from age 5 to age 11 years per unit increase in PM_{10} (~3.8ml yr^{-1}), and 14ml per unit increase of NO_2 exposure (~2.3ml yr^{-1}). In addition, we observed significant associations of PM_{10} and NO_2 exposures with post-bronchodilator FEV_1. In cross-sectional analyses, using a detailed assessment of summer and winter pollutant exposure at age 11 years, we found no associations between air pollution and contemporaneous measures of lung function.

One of the strengths of this study was the use of the comprehensive validated MEEM model to estimate exposures for cross-sectional analyses of outcomes at 11 years of age. This model provided weighted estimates of exposure based on time-activity patterns and NO_2 and PM_{10} models with a high spatio-temporal resolution. Ideally, we would have used MEEM to estimate lifetime exposure of each child. However, MEEM requires detailed descriptions of the house design that were not available longitudinally for the ~ 50% of children who had moved house from their original home during follow up. Therefore we used the 'lifetime model', a slightly simplified version of MEEM that did not require detailed knowledge of the home environment to estimate exposures on a monthly basis from birth to age 11 years for longitudinal analyses. The ranges of exposures estimated by MEEM (9.7-28.0μg/m³ and 6.5-38.1μg/m³ for PM_{10} during the previous summer and winter, respectively, and 9.5-43.0μg/m³ and 10.3-47.2μg/m³ for NO_2, respectively) were greater than the corresponding estimates from the lifetime model at age 10-11 years (PM_{10}: 8.8-14.0μg/m³; NO_2: 10.8-23.7μg/m³). Differences between estimates from each model reflect the different time periods used for averaging (3-month averages during summer and winter for MEEM, 12-month averages at age 10-11 for the lifetime model) and the use of the INDAIR model to estimate indoor exposures for MEEM, which captures peaks in exposure due to gas cooking and cigarette smoking, as well as very low exposures due to low air exchange rates. However, the lifetime model also improves over previously used exposure assessment methods by providing retrospective estimates of monthly exposures that can be aggregated into different exposure time windows for longitudinal and cross-sectional analyses. Furthermore, using home and school address histories, we modelled exposure at an individual level, rather than a community level, thereby reducing the potential for exposure mis-classification.

Due to the strong correlation between NO_2 and PM_{10} exposures in our study, we used single rather than two pollutant models. Many previous cohort studies of air pollution have included cigarette smoking and socio-economic status as confounders in their analysis (Brunst et al. 2012; Li et al. 2000; Stocks et al. 2003). Although it is likely that parental smoking and socio-economic status affect lung function in children, we did not include them in our final model, because they were not significant predictors of the outcomes and we therefore assumed that they did not confound associations with air pollution exposures in our study. However, we cannot rule out residual confounding by these or other exposures. In addition we acknowledge that our estimates of PM_{10} exposures do not necessarily represent the size fraction of particulate matter that is most damaging and that further studies of associations with fine or ultra fine particles are needed to address this.

Another strength of this study was its setting in the context of a population-based birth cohort with repeated measurements of lung function, an objective outcome that is not affected by recall or reporting bias, at four ages. Assessment of sR_{aw} enabled measurement of lung function from a young age (age 3 years). Assessing bronchodilator responses is a common diagnostic tool to test for reversible airway obstruction that can also be used to estimate the maximum achievable expiratory volume of a child. The results of our longitudinal analyses suggest an average annual growth deficit of 9.8ml yr^{-1} and 3.3ml yr^{-1} in the maximum achievable expiratory volume with each unit increase in PM_{10} and NO_2 exposure.

A limitation of this study was the relatively small sample sizes for some of the analyses, mostly due to missing exposure data. Exposure data were missing for children who moved outside of the Greater Manchester area and for children with incomplete information on home and school

addresses. However, the loss in precision due to sample size limitations may be partly offset by the use of detailed individual-level estimates of longitudinal exposures.

Most published studies have investigated the association between pollutant exposure and FEV_1 cross-sectionally, i.e. at a single time point only. Some of these studies also reported that PM_{10} or NO_2 exposures were associated with decreases in mean FEV_1, but not at a statistically significant level (Avol et al. 2001; Dockery et al. 1989; Oftedal et al. 2008). However, other studies have reported significant negative associations between air pollution exposure and FEV_1 (Gauderman et al. 2000; Gauderman et al. 2004; Horak et al. 2002; Peters et al. 1999; Rojas-Martinez et al. 2007), but often only in subgroups of children, e.g. only in girls (Peters et al. 1999), only in one age group (Gauderman et al. 2004), or only during one season (Horak et al. 2002).

Few studies estimated the longitudinal effects of pollutants on the growth in lung function (Table 4). The Children's Health Study was set in 12 communities of Southern California, USA, with a broad range of pollutant exposures (Gauderman et al. 2000; Gauderman et al. 2004). After 4 years of follow up from age 10 years, increasing community exposure to PM_{10} was associated with a reduced adjusted mean FEV_1 growth rate, with those in the most polluted community having an estimated cumulative reduction in FEV_1 of 3.4% over 4 years compared to those in the least polluted communities (Gauderman et al. 2000). After 8 years of follow up, this association with PM_{10} was no longer statistically significant, although a much higher proportion of the children who lived in high PM_{10} communities had a FEV_1<80% predicted. By age 18 years the average FEV_1 in the community with the highest NO_2 exposure was ~100 ml lower than that seen in the community with the lowest exposure (Gauderman et al. 2004). In a population of 975 Austrian children aged 8 years, who were followed for 3 years, significant negative associations

with lung function growth were reported for winter NO_2 and summer $PM_{10,}$ even though higher concentrations of PM_{10} were present during the winter (Horak et al. 2002). A 3 year study of 3170 children living in Mexico City, which has comparatively high pollution levels, reported statistically significant negative associations of both PM_{10} and NO_2 with growth in FEV_1 (Rojas-Martinez et al. 2007). Specifically, they estimated that an IQR range increase in PM_{10} (36.4μg/m³) was associated with a mean annual deficit in FEV_1 of 29 ml in girls and 27 ml in boys. Similarly, they estimated that an IQR increase in NO_2 (12.0ppb) was associated with a mean annual deficit of 32 ml in girls and 26 ml in boys. When estimates are scaled to the same exposure increment and time period (Table 4) it is apparent that past and present longitudinal studies have estimated a very broad range of effect sizes on lung function growth.

Having found a longitudinal association during childhood, it is interesting to speculate at which time point exposure to pollutants may be most damaging to lung function. The cross-sectional analysis of the detailed NO_2 and PM_{10} exposure estimates derived from MEEM showed no association between exposure and lung function at age 11. However, for post-bronchodilator FEV_1 the cross-sectional analyses indicate that early exposures are associated with poorer lung function (Supplemental Material, Table S4), but this association was not as evident for FEV_1% predicted (Supplemental Material, Table S3). Previous research has suggested that lung development during infancy is particularly susceptible to environmental toxins and that exposure can result in irreversible lung damage (Dietert et al. 2000; Plopper et al. 2000). In the Children's Health Study no significant associations of pollutant exposures were reported for older children (recruited at age 13 years and 15 years) who were also followed longitudinally (Gauderman et al. 2000). However, the majority of epidemiological studies on children's lung function have only assessed current air pollution exposure (Götschi et al. 2008), and very little work has been done

on early life exposure (Oftedal et al. 2008). The results of the present study support the hypothesis that early life exposures may affect lung development in later life.

We found evidence of an impairment in lung function growth at apparently lower exposure levels than previous longitudinal studies of air pollution exposure and lung function in children (Avol et al. 2001; Gauderman et al. 2004; Rojas-Martinez et al. 2007). However, exposure estimates in previous studies are not directly comparable to exposure estimates used in our study, because they were based on levels measured at centrally located outdoor pollution monitors. In contrast, our estimates accounted for both indoor and outdoor exposures, because it is known that children living in urban areas in industrialised countries spend the majority of their time indoors (Infante-Rivard 1993). Our previous work on MEEM has shown that a model allowing for indoor and outdoor exposure provides a better estimate of personal exposure than methods solely based on outdoor air pollution, which tended to overestimate personal exposure (Mölter et al. 2012). Therefore, it is possible that exposure levels assigned to children in previous studies based on outdoor monitors, overestimated their true personal exposures. Nonetheless, the maximum outdoor concentrations of 70-80µg/m³ NO_2 and 60-90µg/m³ PM_{10} found in previous studies in Mexico (Rojas-Martinez et al. 2007) and the US (Avol et al. 2001; Gauderman et al. 2004) do exceed the current regulatory limits for annual mean concentrations in the UK (NO_2= 40µg/m³, PM_{10}=40µg/m³) and are higher than concentrations typically measured at urban background monitoring stations in Manchester (Mölter et al. 2010a; Mölter et al. 2010b).

CONCLUSIONS

Our findings suggest that lifetime exposure to PM_{10} and NO_2 may be associated with reduced growth in FEV_1 in children. Although the observed reductions in FEV_1 growth were small, and

therefore may have little impact on healthy individuals, they could have implications for individuals with chronic respiratory disease, in particular obstructive lung diseases, or in children who go on to smoke cigarettes. Future follow up will provide further insight on whether reductions in FEV_1 growth associated with air pollution persist into adulthood or disappear during adolescence.

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Table 1: Description of study population

Variable	MAAS cohort at birth			Children with longitudinal FEV_1 and longitudinal exposure data			
	N	n or mean	(% or ±SD)	N	n or mean	(% or ±SD)	p[a]
Female gender	1185	543	(45.8)	342	173	(50.6)	0.036
Family history of asthma	1185	441	(37.2)	342	125	(36.5)	0.763
Child is atopic[b]							
age 3	983	225	(22.9)	306	72	(23.5)	0.748
age 5	963	294	(30.5)	334	94	(28.1)	0.241
age 8	927	314	(33.9)	330	100	(30.3)	0.088
age 11	784	281	(35.8)	332	116	(34.9)	0.652
Child has asthma or current wheeze							
age 3	1097	296	(27.0)	330	71	(21.5)	0.007
age 5	1071	297	(27.7)	341	75	(22.0)	0.004
age 8	1023	217	(21.2)	341	65	(19.1)	0.234
age 11	925	214	(23.1)	341	78	(22.9)	0.886
Hospitalisation during first two years of life for lower respiratory tract infection	1185	109	(9.2)	342	34	(9.9)	0.573
Gas cooker in the home							
age 1	1028	801	(77.9)	341	270	(79.2)	0.492
age 8	1029	819	(79.6)	342	270	(78.9)	0.717
age 11	930	727	(78.2)	342	267	(78.1)	0.954
Age at follow up (yrs)							
age 3	1081	3.0	(0.1)	326	3.0	(0.0)	0.208
age 5	1044	5.0	(0.1)	340	5.0	(0.1)	0.008
age 8	976	8.0	(0.2)	339	8.0	(0.1)	0.084
age 11	813	11.4	(0.5)	341	11.4	(0.5)	0.876
Body mass index (kg/m^2)							
age 3	1044	16.7	(1.4)	321	16.7	(1.5)	0.914
age 5	1017	16.3	(1.6)	339	16.4	(1.7)	0.776
age 8	923	17.1	(2.4)	333	17.1	(2.6)	0.643
age 11	816	19.1	(3.4)	341	19.2	(3.4)	0.885

Variable	MAAS cohort at birth			Children with longitudinal FEV_1 and longitudinal exposure data			
	N	n or mean	(% or ±SD)	N	n or mean	(% or ±SD)	p[a]
Short term PM_{10} (µg/m³) 3 day average before review visit							
age 3	1081	21.6	(7.7)	326	21.0	(6.9)	0.186
age 5	1044	21.5	(7.2)	340	21.6	(7.2)	0.910
age 8	976	20.8	(6.2)	339	21.0	(6.0)	0.660
age 11	820	19.6	(9.2)	337	19.7	(9.0)	0.895
Mean Tanner stage	763	2.1	(0.9)	317	2.1	(0.9)	0.648

[a] p value of chi-square test or t-test comparing children with longitudinal FEV_1 and exposure data against all children in the MAAS cohort at birth

[b] determined through skin prick test, mean wheal diameter 3mm greater than negative control for at least 1 out of 9 allergens tested

Table 2: Summary of lung function measures at each review (mean +/-SD)

Lung function measure	**Age 3**	**Age 5**	**Age 8**	**Age 11**
sRaw (kpa/s)[a]	1.10 ±1.23	1.17 ± 1.21	1.22 ±1.23	1.26 ±1.29
FEV_1 (l)		1.05 ± 0.16	1.59 ± 0.25	2.30 ± 0.40
Predicted FEV_1 (l)		1.03 ±0.27	1.60 ± 0.17	2.34 ± 0.29
FEV_1 (as % predicted)		96.4 ±12.7	99.0 ±11.8	98.5 ±11.7
FEV_1 post bronchodilator (as % predicted)		104.9 ±11.3		103.8 ±11.5

[a] Geometric mean (+/-GSD)

Table 3: Results of longitudinal analyses (GEE) of longitudinal PM_{10} and NO_2 exposure (based on the Lifetime model) and lung function and cross-sectional analyses (multivariable linear regression) of PM_{10} and NO_2 exposure at age 10-11 years (based on the Lifetime model or MEEM) and lung function at age 11 years

Exposure metric	**Lung function metric**	**Longitudinal exposure and lung function**				**Exposure at age 10-11 (lifetime model) and lung function at age 11**				**Winter exposure before age 11 review (MEEM) and lung function at age 11**				**Summer exposure before age 11 review (MEEM) and lung function at age 11**			
		β[c]	(95%CI)	p	n[d]	β[c]	(95%CI)	p	n	β[c]	(95%CI)	p	n	β[c]	(95%CI)	p	n
PM_{10} (μg/m^3)	Ln sR_{aw} (kpa/s)[a]	0.009	(-0.027, 0.010)	0.37	453	-0.007	(-0.054, 0.040)	0.77	352	-0.001	(-0.011, 0.008)	0.78	315	0.001	(-0.008, 0.009)	0.90	298
	FEV_1 (as % predicted)[b]	-1.37	(-2.52, -0.23)	0.019	342	-1.13	(-3.36, 1.09)	0.32	373	-0.20	(-0.65, 0.26)	0.39	334	0.07	(-0.33, 0.47)	0.73	317
	FEV_1 after bronchodilator treatment (as % predicted)[b]	-3.59	(-5.36, -1.83)	<0.001	176	-1.71	(-3.94, 0.53)	0.13	366	-0.14	(-0.61, 0.34)	0.57	327	0.15	(-0.27, 0.57)	0.48	310
NO_2 (μg/m^3)	Ln sR_{aw} (kpa/s)[a]	-0.007	(-0.016, 0.003)	0.16	453	0.002	(-0.020, 0.023)	0.88	352	0.001	(-0.004, 0.007)	0.64	315	-0.001	(-0.006, 0.004)	0.57	298
	FEV_1 (as % predicted)[b]	-0.83	(-1.39, -0.28)	0.003	342	-0.83	(-1.79, 0.14)	0.093	373	-0.10	(-0.36, 0.17)	0.47	334	0.05	(-0.18, 0.29)	0.66	317
	FEV_1 after bronchodilator treatment (as % predicted)[b]	-1.20	(-1.97, -0.43)	0.002	176	-1.00	(-1.96, -0.03)	0.043	366	-0.01	(-0.29, 0.27)	0.93	327	0.08	(-0.17, 0.32)	0.53	310

[a]adjusted for age, gender, concurrent body mass index, concurrent atopy, concurrent asthma or wheeze , family history of asthma, hospitalisation during first two years of life for lower respiratory tract infection, average 3-day background PM_{10} concentration prior to sR_{aw} measurement, mean tanner stage

[b] adjusted for age (only in GEE), concurrent atopy, concurrent asthma or wheeze, hospitalisation during first two years of life for lower respiratory tract infection, gas cooker in home, mean tanner stage

[c] β coefficient per 1μg/m³ increase in exposure

[d] number of children included in analysis

Table 4: Comparison of average deficit in lung growth with findings from previously published population-based studies

Author, Year of publication, Country	**Exposure assigned at**	**Study duration**	**Range of exposures (in µg m^{-3})**		**Average deficit in lung growth (in ml yr^{-1}) associated with 1µg m^{-3} increase in exposure[a]**	
			PM_{10}	**NO_2**	**PM_{10}**	**NO_2**
Gauderman et al. 2000, Gauderman et al. 2004, USA	Community level	Age 10-14	20-65	10-70	0.20	0.19
Horak et al. 2002, Austria	Community level	Age 8-11	9-31	2-35	8.4	9.5
Rojas-Martinez et al. 2007, Mexico	Community level	Age 8-11	53-96	54-74	0.80 (girls), 0.74 (boys)	1.4 (girls), 1.1 (boys)
This study, England	Individual level	Birth-Age 11	10-16	15-28	3.8	2.3

[a] Calculated based on published figures, assuming a linear relationship between exposure and lung function.

FIGURE LEGENDS

Figure 1: Outline of exposure assessment showing methods used to estimate concentrations in each microenvironment (with relevant references). The same methods were used at all time points except for the year prior to the age 11 review a detailed indoor model could be used estimating concentrations inside the kitchen, living room and child's bedroom. I/O=Indoor to outdoor ratio; MEEM=Microenvironmental Exposure Model.

Figure 2: Flow diagram of MAAS cohort showing participation rates at each review, the number of lung function measurements collected and the number of exposure estimates available.

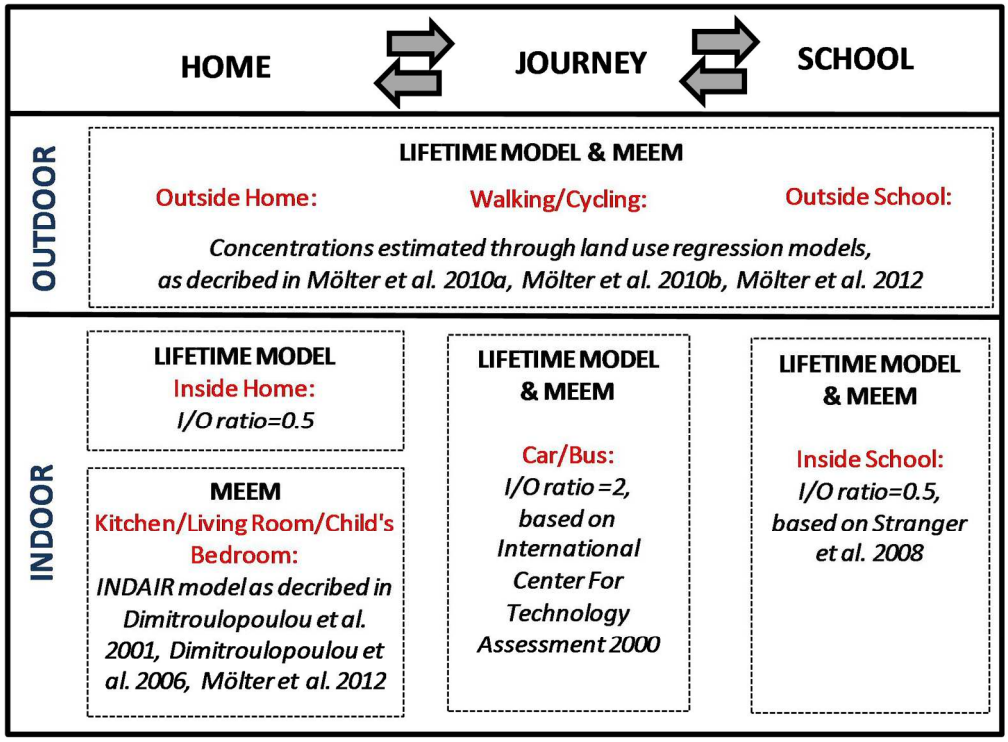

Figure 1

165x122mm (300 x 300 DPI)

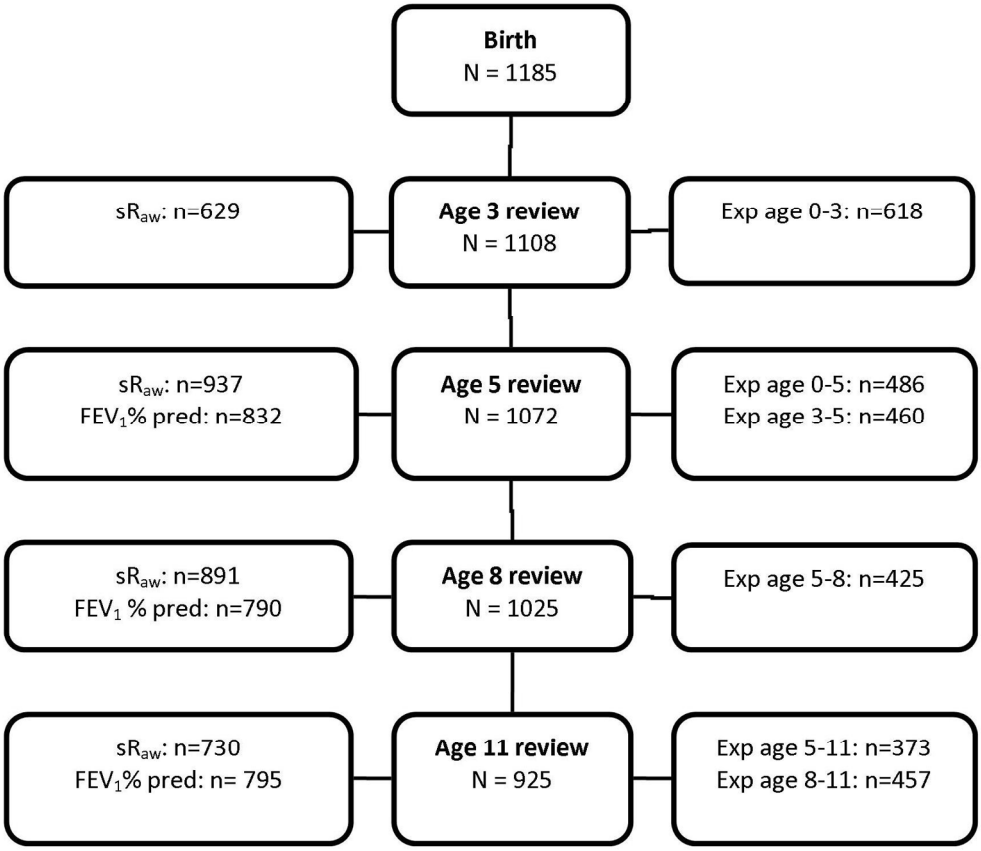

Figure 2

147x125mm (300 x 300 DPI)